Supporting Information

Identification of Purines and 7-Deazapurines as Potent and Selective Type I Inhibitors of Troponin I-Interacting Kinase (TNNI3K)

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Supplementary Table 1. Kinase Selectivity profile for **1**. Compound **1** was examined for inhibition of 203 kinases (human, except as noted) at 10 μM concentration at Ambit Biosciences (ambitbio.com; Karaman, M.W. et al. A quantitative analysis of kinase inhibitor selectivity. *Nat. Biotechnol.* **2008**, *26*, 127-132).

Kinase	% Inhibition	Kinase	% Inhibition	Kinase	% Inhibition
AAK1	89	EPHB4	1	PAK3	1
ABL1	1	ERBB2	1	PAK4	1
ABL2	1	ERBB4	1	PAK6	1
ACVR1	1	ERK1	1	PAK7/PAK5	1
ACVR1B	1	ERK2	1	PCTK1	1
ACVR2A	1	FER	1	PDGFRA	75
ACVR2B	1	FES	1	PDGFRB	97
ACVRL1	1	FGFR1	1	PDPK1	1
ADCK3	1	FGFR2	1	PHKG1	1
ADCK4	1	FGFR3	1	PHKG2	1
AKT1	1	FGFR4	1	PIM1	1
AKT2	1	FGR	1	PIM2	1
AKT3	1	FLT1	1	PKAC-alpha	81
ALK	1	FLT3	1	PKAC-beta	1
AMPK-alpha1	1	FLT4	1	PKMYT1	1
AMPK-alpha2	1	FRK	1	PKN2	1
AURKA	1	FYN	1	PLK1	1
AURKB	1	GAK	98	PLK3	1
AURKC	1	GCN2 $_{S808G}$(Kin.Dom.2)	77	PLK4	1
AXL	1	GSK3A	1	PRKCH	1
BIKE	68	HCK	1	PRKD2	1
BLK	1	IGF1R	1	PRKG1	1
BMPR1A	1	INSR	1	PRKG2	1
BMX	1	INSRR	1	PRKX	1
BRAF	1	ITK	1	PTK2	1
BRSK2	73	JAK1(Kin.Dom.1)	1	PTK2B	1
BTK	1	JAK2(Kin.Dom.2)	1	PTK6	1
CAMK1	1	JNK1	1	RAF1	98
CAMK1D	1	JNK2	1	RET	1
CAMK1G	1	JNK3	1	RIPK2	1
CAMK2A	1	KIT	1	ROS1	1
CAMK2B	1	LCK	1	RPS6KA2(Kin.Dom.1)	1
CAMK2D	1	LIMK1	1	RPS6KA3(Kin.Dom.1)	1
CAMK2G	1	LIMK2	1	RPS6KA4(Kin.Dom.1)	1

CAMKK1	1	LKB1	1	RPS6KA5(Kin.Dom.1)	1
CAMKK2	1	LOK	1	RPS6KA6(Kin.Dom.1)	1
CDK2	1	LTK	1	SLK	1
CDK5	1	LYN	1	SNF1LK2	1
CLK1	67	MAP3K4	1	SRC	1
CLK2	64	MAP3K5	1	SRPK1	1
CLK3	1	MAP4K1	1	STK16	1
CLK4	68	MAP4K3	1	STK33	1
CSF1R	94	MAP4K4	1	STK36	1
CSK	1	MAP4K5	99	SYK	1
CSNK1A1L	1	MARK1	1	TESK1	1
CSNK1D	1	MARK2	1	TGFBR1	1
CSNK1E	1	MARK4	1	TIE2	1
CSNK1G1	1	MERTK	1	TLK1	1
CSNK1G2	1	MET	1	TLK2	1
CSNK2A1	1	MKNK2	70	TNIK	1
CSNK2A2	1	MLK3	1	TNK1	1
DAPK2	1	MRCKA	1	TNK2	1
DAPK3	1	MST1	1	TNNI3K	92
DMPK	1	MST2	1	TRKA	1
DRAK1	99	MST3	1	TRKB	1
DRAK2	1	MST4	1	TRKC	1
EGFR	1	MUSK	1	TTK	1
EPHA1	1	MYLK2	94	TXK	1
EPHA2	1	NDR2	1	TYK2(Kin.Dom.2)	1
EPHA3	1	NEK2	1	TYRO3	1
EPHA4	1	NEK6	1	ULK3(mouse)	1
EPHA5	1	NEK7	1	VEGFR2	1
EPHA6	1	NEK9	1	YANK2	1
EPHA7	1	p38-alpha	1	YANK3	1
EPHA8	1	p38-beta	1	YES	1
EPHB1	1	p38-gamma	1	YSK1	1
EPHB2	1	PAK1	1	ZAP70	1
EPHB3	1	PAK2	1		

Supplementary Table 2. Kinase Selectivity Profile for **7**. Compound **7** was examined for inhibition of 185 kinases ((H) = human, (M) = mouse,) at 10 μM and 35 kinases at 1 μM concentration at Millipore (millipore.com).

Kinase	% Inhibition	Conc. (μM)	Kinase	% Inhibition	Conc. (μM)
ABL(H)	14	10	MINK(H)	53	10
ACK1(H)	39	10	MINK(H)	-2	1
ALK4(H)	-3	10	MKK4(M)	-6	10
ARG(H)	42	10	MKK6(H)	24	10
ARK5(H)	103	10	MKK7-BETA(H)	-24	10
ARK5(H)	13	1	MLCK(H)	34	10
AXL(H)	22	10	MLK1(H)	71	10
BLK(M)	-10	10	MLK1(H)	19	1
BMX(H)	10	10	MNK2(H)	75	10
BRK(H)	-7	10	MNK2(H)	11	1
BRSK1(H)	88	10	MRCK-ALPHA(H)	-17	10
BRSK1(H)	72	1	MRCK-BETA(H)	17	10
BRSK2(H)	21	10	MSK2(H)	37	10
CAMKI-DELTA(H)	35	10	MSSK1(H)	19	10
CAMKII-BETA(H)	28	10	MST1(H)	35	10
CAMKII-DELTA(H)	43	10	MST3(H)	20	10
CAMKII-DELTA(H)	51	10	MUSK(H)	-9	10
CAMKII-DELTA(H)	0	1	NEK11(H)	71	10
CAMKII-DELTA(H)	4	1	NEK11(H)	11	1
CAMKII-GAMMA(H)	36	10	NEK2(H)	0	10
CAMKIV(H)	13	10	NEK3(H)	44	10
CDK1/CYCLINB(H)	13	10	NEK7(H)	17	10
CDK2/CYCLINE(H)	39	10	NLK(H)	85	10
CDK3/CYCLINE(H)	4	10	NLK(H)	20	1
CDK5/P25(H)	13	10	PAK2(H)	-13	10
CDK5/P35(H)	11	10	PAK3(H)	0	10
CDK7/CYCLINH/MAT1(H)	45	10	PAR-1B-ALPHA(H)	38	10
CDK9/CYCLINT1(H)	22	10	PASK(H)	40	10
CK1(Y)	72	10	PDGFR-ALPHA(H)	8	10
CK1(Y)	16	1	PDGFR-BETA(H)	-2	10
CK1-GAMMA1(H)	27	10	PDK1(H)	7	10
CK1-GAMMA2(H)	22	10	PHK-GAMMA2(H)	1	10
CK1-GAMMA3(H)	18	10	PIM-1(H)	8	10
CK2-ALPHA2(H)	91	10	PIM-2(H)	-27	10
CK2-ALPHA2(H)	2	1	PKB-ALPHA(H)	41	10
CKIT(H)	-2	10	PKB-BETA(H)	-18	10
CLK2(H)	79	10	PKB-GAMMA(H)	31	10
CLK2(H)	-9	1	PKC-BETAI(H)	31	10

CLK3(H)	-8	10	PKC-BETAII(H)	-2	10
C-RAF(H)	85	10	PKC-DELTA(H)	50	10
C-RAF(H)	92	1	PKC-EPSILON(H)	13	10
CSRC(H)	0	10	PKC-ETA(H)	27	10
DAPK1(H)	10	10	PKC-GAMMA(H)	-3	10
DAPK2(H)	-29	10	PKC-IOTA(H)	8	10
DCAMKL2(H)	-3	10	PKC-MU(H)	-30	10
DDR2(H)	-5	10	PKC-THETA(H)	-39	10
DMPK(H)	14	10	PKC-ZETA(H)	38	10
DRAK1(H)	96	10	PKD2(H)	-10	10
DRAK1(H)	75	1	PKG1-ALPHA(H)	62	10
DYRK2(H)	20	10	PKG1-ALPHA(H)	-13	1
EEF-2K(H)	-16	10	PKG1-BETA(H)	-31	10
EGFR(H)	12	1	PKG1-BETA(H)	64	10
EPHA1(H)	35	10	PKG1-BETA(H)	28	1
EPHA2(H)	-1	10	PKG1-BETA(H)	28	1
EPHA3(H)	3	10	PLK3(H)	5	10
EPHA4(H)	-28	10	PRK2(H)	71	10
EPHA5(H)	21	10	PRK2(H)	11	1
EPHA7(H)	18	10	PRKX(H)	7	10
EPHA8(H)	9	10	PTK5(H)	16	10
EPHB1(H)	24	10	PYK2(H)	29	10
EPHB2(H)	-12	10	RET(H)	48	10
EPHB3(H)	23	10	RIPK2(H)	66	10
EPHB4(H)	10	10	RIPK2(H)	5	1
ERBB4(H)	-17	10	ROCK-II(H)	89	10
FAK(H)	30	10	ROCK-II(H)	53	1
FER(H)	17	10	RON(H)	29	10
FES(H)	13	10	ROS(H)	2	10
FGFR1(H)	44	10	RSE(H)	2	10
FGFR2(H)	-10	10	RSK2(H)	42	10
FGFR3(H)	14	10	RSK3(H)	45	10
FGFR4(H)	5	10	RSK4(H)	-10	10
FGR(H)	5	10	SAPK2A(T106M)(H)	-9	10
FLT1(H)	-37	10	SAPK2B(H)	59	10
FLT3(H)	62	10	SAPK2B(H)	7	1
FLT3(H)	7	1	SAPK3(H)	-2	10
FLT4(H)	46	10	SAPK4(H)	-1	10
FMS(H)	2	10	SGK(H)	3	10
FRAP1(H)	-5	10	SGK2(H)	-4	10
FRAP1/FKBP12(H)	-5	10	SGK3(H)	31	10
FYN(H)	88	10	SIK(H)	91	10
FYN(H)	16	1	SIK(H)	28	1

GCK(H)	86	10	SNK(H)	7	10
GCK(H)	36	1	SRPK1(H)	36	10
GRK5(H)	-4	10	SRPK2(H)	27	10
GRK6(H)	0	10	STK33(H)	101	10
GRK7(H)	34	10	STK33(H)	-2	1
GSK3-ALPHA(H)	55	10	TAK1(H)	25	10
GSK3-ALPHA(H)	51	1	TAK1(H)	45	10
HASPIN(H)	52	10	TAK1(H)	15	1
HASPIN(H)	9	1	TAO1(H)	57	10
HCK(H)	61	10	TAO1(H)	4	1
HCK(H)	0	1	TAO2(H)	23	10
HIPK1(H)	-6	10	TAO3(H)	40	10
HIPK3(H)	-1	10	TBK1(H)	51	10
IKK-ALPHA(H)	10	10	TBK1(H)	11	1
IKK-BETA(H)	29	10	TEC(H)	21	10
IRAK1(H)	7	10	TIE2(H)	-18	10
IRAK4(H)	21	10	TLK2(H)	13	10
IRR(H)	-12	10	TRKA(H)	75	10
KDR(H)	24	10	TRKA(H)	-9	1
LIMK1(H)	72	10	TRKB(H)	27	10
LIMK1(H)	12	1	TSSK1(H)	32	10
LKB1(H)	-2	10	TSSK2(H)	-1	10
LOK(H)	36	10	TXK(H)	28	10
MAPK1(H)	8	10	ULK2(H)	17	10
MAPK2(H)	5	10	ULK3(H)	37	10
MAPKAP-K3(H)	-15	10	VRK2(H)	31	10
MARK1(H)	36	10	WNK2(H)	7	10
MEK1(H)	14	10	WNK3(H)	7	10
MER(H)	37	10	YES(H)	23	10
MET(H)	19	10	ZAP-70(H)	-24	10
			ZIPK(H)	25	10

Supplementary Table 3. Kinase Selectivity Profile for **48**. Compound **48** was examined for inhibition of 185 kinases ((H) = human, (M) = mouse,) at 10 μM and 10 kinases at 1 μM concentration at Millipore (millipore.com).

Kinase	% Inhibition	Conc. (μM)	Kinase	% Inhibition	Conc. (μM)
ABL(H)	46	10	MINK(H)	7	10
ACK1(H)	90	10	MKK4(M)	19	10
ACK1(H)	34	1	MKK6(H)	41	10
ALK4(H)	-12	10	MKK7-BETA(H)	0	10
ARG(H)	53	10	MLCK(H)	0	10
ARG(H)	-23	1	MLK1(H)	16	10
ARK5(H)	31	10	MNK2(H)	9	10
AXL(H)	1	10	MRCK-ALPHA(H)	-15	10
BLK(M)	33	10	MRCK-BETA(H)	-7	10
BMX(H)	48	10	MSK2(H)	-10	10
BRK(H)	-2	10	MSSK1(H)	3	10
BRSK1(H)	-8	10	MST1(H)	-5	10
BRSK2(H)	22	10	MST3(H)	-12	10
CAMKI-DELTA(H)	1	10	MUSK(H)	0	10
CAMKII-BETA(H)	7	10	NEK11(H)	55	10
CAMKII-DELTA(H)	1	10	NEK11(H)	9	1
CAMKII-GAMMA(H)	21	10	NEK2(H)	-24	10
CAMKIV(H)	13	10	NEK3(H)	-4	10
CDK1/CYCLINB(H)	-5	10	NEK7(H)	-11	10
CDK2/CYCLINE(H)	0	10	NLK(H)	77	10
CDK3/CYCLINE(H)	8	10	NLK(H)	-2	1
CDK5/P25(H)	1	10	PAK2(H)	-6	10
CDK5/P35(H)	9	10	PAK3(H)	-40	10
CDK7/CYCLINH/MAT1(H)	-5	10	PAR-1B-ALPHA(H)	4	10
CDK9/CYCLINT1(H)	30	10	PASK(H)	6	10
CK1(Y)	3	10	PDGFR-ALPHA(H)	-28	10
CK1-GAMMA1(H)	4	10	PDGFR-BETA(H)	3	10
CK1-GAMMA2(H)	-1	10	PDK1(H)	-9	10
CK1-GAMMA3(H)	-3	10	PHK-GAMMA2(H)	-24	10
CK2-ALPHA2(H)	7	10	PIM-1(H)	-3	10
CKIT(H)	9	10	PIM-2(H)	-7	10
CLK2(H)	-11	10	PKB-ALPHA(H)	2	10
CLK3(H)	-18	10	PKB-BETA(H)	-19	10
C-RAF(H)	96	10	PKB-GAMMA(H)	-3	10
C-RAF(H)	91	1	PKC-BETAI(H)	-6	10
CSRC(H)	12	10	PKC-BETAII(H)	0	10
DAPK1(H)	-11	10	PKC-DELTA(H)	1	10
DAPK2(H)	13	10	PKC-EPSILON(H)	0	10

DCAMKL2(H)	15	10	PKC-ETA(H)	-9	10
DDR2(H)	-3	10	PKC-GAMMA(H)	14	10
DMPK(H)	1	10	PKC-IOTA(H)	8	10
DRAK1(H)	11	10	PKC-MU(H)	-1	10
DYRK2(H)	5	10	PKC-THETA(H)	-5	10
EEF-2K(H)	3	10	PKC-ZETA(H)	-13	10
EPHA1(H)	6	10	PKD2(H)	11	10
EPHA2(H)	-11	10	PKG1-ALPHA(H)	-5	10
EPHA3(H)	1	10	PKG1-BETA(H)	2	10
EPHA4(H)	8	10	PLK3(H)	-25	10
EPHA5(H)	12	10	PRK2(H)	-1	10
EPHA7(H)	-18	10	PRKX(H)	8	10
EPHA8(H)	1	10	PTK5(H)	33	10
EPHB1(H)	5	10	PYK2(H)	7	10
EPHB2(H)	-36	10	RET(H)	5	10
EPHB3(H)	3	10	RIPK2(H)	43	10
EPHB4(H)	-2	10	ROCK-II(H)	-1	10
ERBB4(H)	1	10	RON(H)	0	10
FAK(H)	6	10	ROS(H)	6	10
FER(H)	-4	10	RSE(H)	-6	10
FES(H)	-6	10	RSK2(H)	28	10
FGFR1(H)	8	10	RSK3(H)	28	10
FGFR2(H)	0	10	RSK4(H)	8	10
FGFR3(H)	5	10	SAPK2A(H)	69	10
FGFR4(H)	-8	10	SAPK2A(H)	13	1
FGR(H)	9	10	SAPK2B(H)	79	10
FLT1(H)	6	10	SAPK2B(H)	26	1
FLT3(H)	-11	10	SAPK3(H)	-8	10
FLT4(H)	31	10	SAPK4(H)	7	10
FMS(H)	8	10	SGK(H)	-14	10
FRAP1(H)	8	10	SGK2(H)	9	10
FRAP1/FKBP12(H)	-12	10	SGK3(H)	7	10
FYN(H)	46	10	SIK(H)	84	10
GCK(H)	20	10	SIK(H)	42	1
GRK5(H)	-5	10	SNK(H)	-1	10
GRK6(H)	-4	10	SRPK1(H)	-16	10
GRK7(H)	5	10	SRPK2(H)	-6	10
GSK3-ALPHA(H)	21	10	STK33(H)	-8	10
HASPIN(H)	-1	10	TAK1(H)	11	10
HCK(H)	-9	10	TAO1(H)	44	10
HIPK1(H)	-6	10	TAO2(H)	11	10
HIPK3(H)	1	10	TAO3(H)	39	10
IKK-ALPHA(H)	0	10	TBK1(H)	4	10

IKK-BETA(H)	14	10	TEC(H)	-4	10
IRAK1(H)	-10	10	TIE2(H)	-4	10
IRAK4(H)	-14	10	TLK2(H)	-1	10
IRR(H)	8	10	TRKA(H)	7	10
KDR(H)	13	10	TRKB(H)	14	10
LIMK1(H)	70	10	TSSK1(H)	-14	10
LIMK1(H)	30	1	TSSK2(H)	0	10
LKB1(H)	1	10	TXK(H)	38	10
LOK(H)	76	10	ULK2(H)	12	10
LOK(H)	20	1	ULK3(H)	-2	10
MAPK1(H)	0	10	VRK2(H)	15	10
MAPK2(H)	-1	10	WNK2(H)	-4	10
MAPKAP-K3(H)	4	10	WNK3(H)	3	10
MARK1(H)	15	10	YES(H)	4	10
MEK1(H)	10	10	ZAP-70(H)	-4	10
MER(H)	0	10	ZIPK(H)	7	10
MET(H)	-12	10			

Supplementary Table 4. Statistics for X-ray crystal structures.

	Data Collection	
	TNNI3K-**1**	TNNI3K-**53**
Space group	$P2_1$	$P2_1$
Cell dimensions (a,b,c) (Å)	80, 115, 92	85, 106, 93
Angles (°)	90, 92, 90	90, 94, 90
Resolution (Å)	2.7	3.2
Completeness (%)	97	99
R_{sym} (%)	7.5	9.9
Mean I/σ	27	20
Redundancy	3.7	3.4
Wavelength (Å)	1.54	1.54
	Refinement	
Resolution range	38-2.7	50-3.2
Reflections	42439	25851
R_{work}	21.5	20.8
R_{free}	26.1	25.1
R.m.s. dev. Bonds		
Lengths (Å)	0.009	0.007
Angles (°)	1.27	1.23